

REMARKS

Claims 1, 2, 4, 5, 8, and 22 are pending in the application. Claim 4 stands withdrawn. Claims 1, 2, 5, 8, and 22 are currently under examination.

Applicants gratefully acknowledge the Examiner's withdrawal of the rejection of the pending claims under 35 USC § 112, second paragraph made in section 7 of the previous Office Action.

A Declaration under 37 C.F.R. § 1.132 by Margot M. O'Toole is attached to this response.

Reconsideration of the rejections of record and allowance of this application is respectfully requested.

**Amendments to the claims**

Claim 1 has been amended to more clearly express that which applicants consider their invention. It is believed that no new matter has been added to the application.

**Claim rejections**

**35 U.S.C. § 112, first paragraph rejections**

Claims 1, 2, 4, 5, 8, and 22, all the claims pending in the application, stand rejected under 35 U.S.C. § 112, first paragraph, allegedly because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claims.

Claim 1, the only independent claim pending in the application, recites a method of identifying an increased likelihood of lupus nephritis in a human or a mouse. The method comprising detecting an expression level of midkine gene in a kidney sample isolated from a human or a mouse and comparing the detected expression level of midkine gene with a reference. Claim 1 and claims 2, 5, 8, and 22 which depend from claim 1, were rejected for allegedly lacking enablement based on Kotzin (Cell, 1996, 85:303-306; referred to herein as "Kotzin 1"), Kotzin (J. Clin. Invest., 1997, 99:557-558; referred to herein as "Kotzin 2"), Liu *et al.* (Clin. Immunol., 2004, 112:225-230; referred to herein as "Liu"), and Morel *et al.* (PLoS Biol., 2004, 2:1061-1064; referred to herein as "Morel").

The Office Action, referencing Kotzin 1, Kotzin 2, Liu, and Morel, alleges that due to the “high level of unpredictability in the art and the lack of guidance provided by the specification and prior art, undue experimentation would be required to practice the claimed invention.” Specifically, the Office Action alleges that the “specification has not provided sufficient guidance to extrapolate the [animal] results to human.” (See page 9 of the Office Action.)

Applicants respectfully traverse the rejection and the reasoning and comments provided in support thereof, and provide the following comments in response thereto.

The Examiner cites Kotzin 1 and Kotzin 2 for teaching that: (1) the underlying cause of lupus has yet to be determined, (2) it seems likely that different genetic contributions are operative in different animal models, and (3) environmental factors and phenotypic expression are varied in human patients. At page 7 of the Office Action, the Examiner asserts that Kotzin indicates that “...an animal model may not be an accurate representation of another animal’s response to lupus...[and that]...[g]enetic homology does not necessarily correlate to phenotypic expression.” Applicants submit that the invention does not claim that a change in midkine expression means that a human will necessarily develop lupus. Also, the invention does not claim midkine expression as a direct cause of lupus. The invention does not claim midkine expression as definitely leading to phenotypic expression of lupus. Instead, the claims are drawn to elevated midkine gene expression as associated with an increased likelihood of lupus. As stated at point 4 of the Declaration under 37 C.F.R. § 1.132 by Margot M. O’Toole, included herewith “[b]ased on my reading of the Kotzin references, nothing in Kotzin 1 suggests a lack of correlation between elevated midkine gene expression and increased likelihood of lupus in humans.”

Nothing in Kotzin 1 suggests a lack of correlation between elevated midkine gene expression and increased likelihood of lupus. Furthermore, Kotzin 1 specifically teaches that animal models have contributed greatly to the elucidation of systemic lupus erythematosus pathogenesis in humans. (See page 303, column 2, first paragraph.) For example, Kotzin 1 teaches identification of autoantibodies and their presence in lupus in **patients and mice**. (See page 303, second column, second paragraph, through page 304, first column, first paragraph; emphasis added.) Furthermore, Kotzin 1 states “in lupus patients **and** lupus mice, studies have repeatedly shown that a subset of anti-DNA antibody-producing B cells are

clonally expanded and that their immunoglobulin genes are modified by somatic mutation." (See page 304, first column, second paragraph; emphasis added.) Thus, contrary to the Examiner's assertions, Applicants submit that Kotzin 1 does, in fact, support extrapolation of genetic characteristics in lupus mice to humans with lupus.

Kotzin 2 teaches that NZB X NZW mice are "one of the best-studied models of lupus nephritis." (See for example, page 557, second column, last paragraph.) NZB X NZW mice are one of the strains shown in the application to have elevated levels of midkine gene expression correlating with lupus. (See Figure 4 of the specification as filed.) Thus, contrary to the Examiner's assertions, Applicants submit that Kotzin 2 does, in fact, support extrapolation of genetic characteristics of lupus in mice to humans with lupus. Furthermore, and as stated at point 5 of the Declaration under 37 C.F.R. § 1.132 by Margot M. O'Toole, included herewith "[t]he signs and symptoms exhibited by these mice closely parallels those observed in humans with lupus.' and "I believe that Kotzin 2 does, in fact, support extrapolation of genetic characteristics of lupus in mice to humans with lupus."

The Examiner cites Morel for teaching that one cannot directly apply data obtained from animal models to human disease because "...human autoimmune diseases...show extremely heterogenous **clinical presentation**...[and that]...the mouse model only provides a partial representation of the real biological complexity underlying the human disease..." (See page 8 of the Office Action, emphasis added.) Again, Applicants respectfully submit that these observations are irrelevant to what is presently claimed, i.e., a method of identifying an increased likelihood of lupus nephritis associated with an elevated midkine gene expression. Morel does nothing to contradict or dispute the present disclosure which supports the extrapolation of genetic characteristics in lupus mice to humans with lupus. Morel is cited for the proposition that human autoimmune diseases show extremely heterogeneous **clinical presentation** and that animal models only present a simplified version.

Liu is cited for teaching that correlation of gene expression in mice is not indicative of correlation of gene expression in humans. Liu is directed to correlation of gene expression in autoimmune patients with NOD and NZM mice. In contrast, the data in the instant specification shows a positive correlation of midkine gene expression with lupus in MRL/MPJ-Fas<sup>lpr</sup>, MRL/MPJ, and NZB X NZW F1 mice. (See, for example Figures 2, 3, and 4 of the specification as filed.) Specifically, "[t]he

present invention identifies MDK as a marker of SLE and LN, which is differentially expressed in kidneys of LN-affected MRL/MPJ-Fas<sup>lpr</sup>, MRL/MpJ, and NZB X NZW F1 mice, relative to kidney samples from control C57BL/6 and C57BL/6-Fas<sup>lpr</sup> mice.” (See paragraph 0079 at page 22 of the Specification as filed.) Thus, Liu’s observations in NOD and NZM mice, neither of which is necessarily a good model of SLE, do not refute that the results observed in the present application may be extrapolated to humans. According to point 6 of the Declaration under 37 C.F.R. § 1.132 by Margot M. O’Toole, included herewith, “[n]either of these two mouse strains is necessarily a good model of lupus nephritis because the NOD mouse strain is a model for diabetes and the NZM mouse strain does not necessarily develop lupus symptoms.”

Furthermore, Applicants submit herewith a report by Furukawa and Yoshimasu (Autoimmun. Rev., 2005, 4:345-350; referred to herein as Furukawa, and attached as Exhibit A). Furukawa refers to the development of MRL/lpr mice, which have a mutation in the Fas gene. Furukawa states “[t]he Fas-defect is believed to accelerate the autoimmunity of MRL/lpr mice, and results in lupus nephritis....” (See page 347, first column, first paragraph; emphasis added.) Furukawa states that “[f]rom these studies, it is concluded that the lpr mutation accelerates the progression of a mild type of systemic and cutaneous connective tissue disease into a more severe one such as SLE.” (See page 347, second column, second paragraph.) At point 8 of the Declaration under 37 C.F.R. § 1.132 by Margot M. O’Toole, included herewith, Dr. O’Toole states “I believe that Furukawa supports extrapolation of genetic characteristics in lupus mice to humans with lupus.” Thus, Applicants submit that Furukawa supports extrapolation of genetic characteristics in lupus mice to humans with lupus.

The enablement requirements are detailed in the MPEP § 2164. MPEP § 2164.0 states:

The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int’l Trade Comm’n 1983), aff’d. sub nom., *Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976).

Moreover, according to the MPEP § 2164.02 “[i]f the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate.” Applicants submit that genetic information gathered from murine models for lupus is recognized as applicable to humans with lupus.

In MPEP § 2164.04, the guidelines for rejecting a claim for lack of enablement state “[t]he language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation”. Applicants submit that, given the level of knowledge and skill in the art no undue experimentation is necessary to practice the method of the invention. Claim 1, the only independent claim, is to a method of identifying an increased likelihood of lupus nephritis in a human or a mouse. The method comprising detecting an expression level of midkine gene in a kidney sample isolated from a human or a mouse and comparing the detected expression level of midkine gene with a reference. The specification also teaches that midkine (MDK) gene and protein are found in humans. (See for example paragraphs 0070 at page 19 and 0075 at page 21 of the specification as filed.) The specification shows that the level of midkine mRNA is correlated with disease in MRL/Fas<sup>lpr</sup> and NZB X NZW F1 lupus mouse models. As discussed above, these two mouse models are good models of lupus nephritis. It would not be undue experimentation to measure the levels of midkine gene expression in a human or mouse of interest and to compare the levels of midkine gene expression with a reference to determine whether or not the mouse or human of interest has an increased likelihood of lupus nephritis. Applicants submit that the specification teaches how to make and use the claimed invention without undue experimentation.

In sum, Applicants submit that those of skill in the art would recognize that the results obtained with the mouse models used in the present application (namely MRL/Fas<sup>lpr</sup> and NZB X NZW F1) are applicable to humans with lupus for the reasons noted. The references cited by the Examiner, in fact show correlation between the genetic findings in lupus mice with humans with lupus. Kotzin 1 for example, describes the presence of autoimmune antibodies in humans with systemic lupus erythematosus **and** in lupus mice. Kotzin 2 teaches that NZB X NZW mice are “one of the best-studied models of lupus nephritis.” Also, in the instant application the

levels of midkine gene expression correlate with lupus nephritis in MRL/Fas<sup>lpr</sup> and NZB X NZW F1 mice. These two strains are noted above as being good models for lupus nephritis in humans. Furthermore, Margot M. O'Toole, in point 2 of the Declaration under 37 C.F.R. § 1.132 included herewith, states “[t]he MRL/MPJ-Fas<sup>lpr</sup> and NZB X NZW F1 strains of lupus nephritis-affected mice are extensively used in the art to study lupus disease. The signs and symptoms exhibited by these mice closely parallel those observed in humans with lupus, ..” The comments by Margot M. O'Toole, Kotzin 2, and Furukawa support correlation between the genetic findings in lupus mice with humans with lupus.

In rejecting the claims, the Examiner has cited numerous references to the fact that a human might not develop disease based on what is observed in mice in part, because disease phenotype among mice is much more uniform compared to the relatively heterogeneous disease expression in patients. (See page 6 of the Office Action.) Applicants submit that the invention does not claim that a change in midkine expression means that a human will necessarily develop lupus. Also, the invention does not claim midkine expression as a direct cause of lupus or as definitely leading to phenotypic expression of lupus. Instead, the claims are drawn to elevated midkine gene expression as associated with an increased likelihood of lupus.

Thus, contrary to the Examiner's assertions, Applicants submit that the references cited do, in fact, support extrapolation of genetic characteristics of lupus mice to humans with lupus.

In view of the foregoing, withdrawal of the rejection under 35 USC § 112, first paragraph, is respectfully requested.

CONCLUSION

In view of the above remarks Applicants respectfully submit that the application is ready for allowance, and such allowance is respectfully requested. However, the Examiner is invited to contact the undersigned agent if any outstanding issues remain.

During the pendency of this application please treat any reply requiring a petition for extension of time for its timely submission as containing a request therefore for the appropriate length of time. The Commissioner is hereby authorized to charge all required extension of time fees during the entire pendency of this application to Deposit Account No. 01-1425.



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# EXHIBIT A